Effect of Exercise and Diet on Triglyceride Metabolism in Rats with Moderate Insulin Deficiency

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SUMMARY

The ability of exercise and diet to modify the effects of moderate streptozotocin-induced insulin deficiency on triglyceride metabolism has been studied in the rat. Insulin-deficient rats allowed to run spontaneously in exercise wheel cages had significantly lower ($P < 0.001$) plasma glucose levels (187 ± 19 mg/dl) than either sedentary (374 ± 24 mg/dl) or sucrose-fed (450 ± 13 mg/dl) diabetic rats, despite the fact that plasma insulin levels were comparable in all these groups. Plasma triglyceride (TG) levels in exercise-trained rats with diabetes (51 ± 5 mg/dl) were actually lower than in control rats with normal glucose tolerance (90 ± 14 mg/dl). In contrast, plasma TG levels were higher than control levels in diabetic sedentary rats (128 ± 11 mg/dl), and severe hypertriglyceridemia developed in sucrose-fed diabetic rats (369 ± 35 mg/dl). The ability of exercise training to attenuate diabetic hypertriglyceridemia, which was observed in both chow-fed and sucrose-fed rats, was secondary to a decrease in TG secretion, and appeared to be related to lower plasma FFA concentrations. In contrast, the accentuation of diabetic hypertriglyceridemia seen in sucrose-fed rats was related to a defect in TG catabolism. Adipose tissue lipoprotein lipase (LPL) activities were essentially identical in all diabetic rats, suggesting that the observed difference in TG kinetics could not be attributed to concomitant increases or decreases in adipose tissue LPL activity. These results emphasize the powerful impact of exercise and diet on TG metabolism in rats with moderate degrees of insulin deficiency. DIABETES *32*:46–50, January 1983.

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Previous studies have indicated that plasma triglyceride (TG) concentrations are profoundly altered when normal rats are allowed to run spontaneously. Thus, exercise training lowers plasma TG levels in chow-fed rats,[1,2] markedly attenuates carbohydrate-induced hypertriglyceridemia in sucrose- and glucose-fed rats,[2] and prevents the rise in plasma TG levels that occurs as normal rats age.[3] In contrast, high carbohydrate diets have the opposite effect and produce marked hypertriglyceridemia when given to normal rats.[2,4,5] These results emphasize the profound impact that environmental manipulation can have on TG metabolism in normal animals, and raise questions as to the effect that these variables might have in states associated with abnormal TG metabolism. A prime example of such a situation is streptozotocin (SZ)-induced diabetes in the rat, which is characterized by hypertriglyceridemia.[6,7] Given the observation that hypertriglyceridemia is also a common finding in human diabetes,[8,9] it seemed worthwhile to define the effects of exercise training and dietary carbohydrate on TG metabolism in rats with a moderate degree of SZ-induced hypertriglyceridemia. The results to be presented indicate that both experimental interventions profoundly modulate plasma TG concentrations, and help to define the mechanism by which these changes occur.

MATERIALS AND METHODS

Male, 6-wk-old Sprague-Dawley rats were maintained on a 12-h dark (1800–0600)-light (0600–1800) cycle and allowed free access to food and water. Insulin-deficient diabetes was induced by intravenous injection of SZ, 40 mg/kg, diluted in 0.01 M citrate buffer (pH 4.5). Control rats were injected with vehicle. Plasma glucose[10] of SZ-injected rats was determined 3 days later at 1400 h (6 h after food withdrawal), and diabetic rats divided into groups with similar means and ranges of plasma glucose concentrations. Two series of rats were studied. In the first group of experiments, diabetic rats

were divided into three groups. One group was maintained in standard laboratory cages, and fed conventional chow, containing (as percent calories) 60% vegetable starch, 29% protein, and 11% fat. The second group was also housed in standard cages, but fed a diet (Teklad Labs, Madison, Wisconsin) which contained 66% sucrose, 22% protein, and 12% fat. The rats in the third group were allowed to run spontaneously in exercise wheel cages (Wahman Co., Timonium, Maryland), and fed conventional rat chow. Initial values of plasma glucose concentration were 307 ± 15, 304 ± 18, and 312 ± 14 mg/dl in the three groups, respectively.

A second series of experiments was performed in which diabetic rats were divided into four groups: sedentary, chow-fed; exercise-trained, chow-fed; sedentary, sucrose-fed; and exercise-trained, sucrose-fed. Initial values (mean ± SEM) for plasma glucose were 279 ± 24, 276 ± 19, 276 ± 18, and 287 ± 20 mg/dl, in the four groups, respectively.

All experiments were performed 21 days later, starting at 1400 h, 6 h after withdrawal of food. Blood samples were collected from the tail, and plasma separated by centrifugation for measurement of plasma glucose,[10] TG,[11] insulin,[12] and FFA[13] concentrations.

Very-low-density-lipoprotein (VLDL)-TG turnover rates were estimated by determining the rates at which VLDL-TG isolated from experimental donor rats were removed following their injection into normal recipient rats. This approach, which has been previously described in detail,[14] is carried out as follows. Food was removed at 0800 h from the experimental donor rats, and these animals were injected via the tail vein with 500 μCi of ^{3}H-glycerol at 1400 h. Donor rats were then exsanguinated under sodium thiamylal anesthesia 40 min later. Plasma was dialyzed overnight against 0.15 M NaCl at 4°C, and aliquots containing equal amounts of TG were injected into the normal recipient rats the next day at 1400 h. After administration of plasma containing prelabeled VLDL-TG, the tail was amputated proximal to the site of injection, and blood collected 2, 4, 6, and 8 min after injection. The plasma was separated by centrifugation and stored frozen until analyzed. Samples were extracted by the Folch method,[15] polar lipids were removed by silic acid, and the TG fraction was evaporated to dryness. Radioactivity was measured by liquid scintillation counting (Beckman LS-9000), using a standard toluene mixture. The half-time ($t_{1/2}$) of VLDL-TG removal was directly determined from these measurements by a least square linear regression analysis, and VLDL-TG turnover rate was calculated from the following formula:

$$\text{VLDL-TG turnover rate} = (1n\ 2 \div t_{1/2}) \times (\text{plasma TG concentration}) \times (\text{plasma volume}).$$

Since these studies were carried out under steady-state conditions, VLDL-TG turnover rate = VLDL-TG secretion rate. During the remainder of this communication, this measurement will be referred to as the VLDL-TG secretion rate.

Adipose tissue lipoprotein lipase (LPL) activity of epididymal fat pads was assayed by using minor modifications[16] of the method of Schotz et al.[17] Adipose tissue homegenates were prepared in ice-cold 0.25 M sucrose-1 mM EDTA buffer (1:4, wt:vol, pH 7.4) from both left and right epididymal fat pads, using ground glass-on-glass homogenizing equipment. Homogenates were centrifuged at 12,000 × *g* for 15 min at 4°C, and the postmitochondrial supernatant aspirated and stored at −70°C. The substrate was C^{14} triolein, and lysolecithin was added as an emulsifier. LPL activity was defined as the amount activated by fasting human serum and inhibited by 1.0 M NaCl. Adipose cell size and number was determined by the osmium-fixation method of Hirsch and Gallian,[18] and protein according to the method of Lowry et al.[19]

RESULTS

In the first series of experiments, the diabetic exercise-trained rats ran 3.2 ± 0.6 (mean ± SEM) miles/day, and gained an average of 66 g during the experimental period. Similar rates of weight gain were seen in normal control (67 g) and sedentary diabetic rats (66 g) fed chow. In contrast, diabetic rats fed sucrose only gained an average of 42 g, which was significantly lower than the other three groups ($P < 0.01$).

Plasma insulin and glucose levels for these experimental groups are seen in Figure 1. Plasma insulin levels were reduced comparably in the three groups of diabetic rats, and the decline in insulin levels of approximately 50% was statistically significant ($P < 0.01$).

The fall in circulating insulin level produced by SZ-injection led to hyperglycemia in all three groups of diabetic rats. However, it is obvious from Figure 1 that the magnitude of the increase was markedly altered by both exercise training and diet, and that these differences were seen in spite of the fact that insulin levels in the three diabetic groups were similar. Thus, glucose levels in sedentary diabetic rats were more than double those of the normal control rats ($P < 0.001$). On the other hand, plasma glucose concentrations in diabetic rats allowed to exercise were not significantly elevated over those seen in nondiabetic control animals, and markedly lower than the levels attained in sedentary diabetic rats ($P < 0.001$). In marked contrast was the impact of feeding simple sugar to diabetic rats. Diabetic sucrose-fed rats had

FIGURE 1. Effect of exercise and diet on mean (±SEM) plasma insulin and glucose concentration in control (C), sedentary, diabetic (D-S), exercise-trained, diabetic (D-ET), and sucrose-fed, diabetic (D-SF) rats. The numbers in parentheses indicate the number of rats in each experimental group.

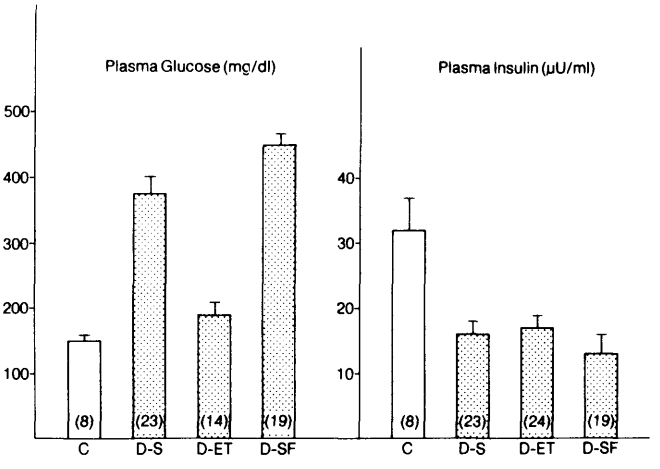

TABLE 1
Mean (±SEM) plasma triglyceride (TG) concentration, triglyceride secretion rate (TG-SR), and adipose tissue lipoprotein lipase (LPL) activity

Group	TG (mg/dl)	TG-SR (mg/min)	LPL activity (nmol FFA released/h)*		
			Pad	$\times 10^6$ cells	mg protein
Control (8)	90 ± 14	3.17 ± 0.47	33 ± 5	2.4 ± 0.4	1.6 ± 2.0
Diabetic-sedentary (21)	128 ± 11	3.11 ± 0.28	8 ± 1	1.0 ± 0.1	0.6 ± 0.1
Diabetic-sucrose (19)	369 ± 35	2.97 ± 0.24	11 ± 1	1.2 ± 0.2	0.8 ± 0.1
Diabetic-exercised (14)	51 ± 5	2.24 ± 0.2	10 ± 1	0.9 ± 0.1	0.6 ± 0.1

Numbers of animals are in parentheses.
*LPL activity was based upon measurement of 10–12 rats/group. LPL activity of the three diabetic groups was significantly reduced ($P < 0.01$–0.001) by all estimates.

significantly higher ($P < 0.02$) glucose concentrations than did diabetic rats fed conventional rat chow.

The effect of these various treatments on plasma TG concentrations, VLDL-TG secretion rates, and adipose tissue LPL is seen in Table 1. These results indicate that plasma TG levels in sedentary diabetic rats were significantly elevated ($P < 0.02$) over control values, without any change in VLDL-TG secretion rates being observed. Thus, hypertriglyceridemia in sedentary diabetic rats must have been secondary to a defect in the removal of VLDL-TG from plasma. The data in Table 1 also demonstrate that sucrose feeding dramatically accentuates the hypertriglyceridemia seen in sedentary diabetic rats. Furthermore, since there is no difference in the VLDL-TG secretion rates of chow-fed and sucrose-fed diabetic rats, the increase in the magnitude of hypertriglyceridemia in sucrose-fed rats must be due to an exaggeration of the defect in VLDL-TG catabolism associated with insulin deficiency.

Finally, these data indicate that plasma TG concentrations were significantly lower ($P < 0.001$) in diabetic rats that were allowed to run as compared with those who were sedentary. Indeed, diabetic exercise-trained rats had plasma TG levels that were even lower than those seen in normal control rats ($P < 0.01$). Stated more simply, exercise training totally abolished diabetic hypertriglyceridemia. The data in Table 1 also demonstrate that VLDL-TG secretion rates were lower ($P < 0.02$) in diabetic exercise-trained rats than in either sedentary diabetic rats or nondiabetic control rats. In other words, the lowering of TG concentrations in diabetic rats allowed to exercise was associated with an exercise-induced fall in VLDL-TG secretion.

It seems apparent from the data in Table 1 that defects in VLDL-TG catabolism account for the variations in the magnitude of hypertriglyceridemia observed in insulin-deficient rats fed either chow or sucrose. However, these results suggest that differences in adipose tissue LPL activity cannot, by themselves, account for the decrease in VLDL-TG removal from plasma seen in rats with insulin-deficient diabetes. These data demonstrate that adipose tissue LPL activity, no matter how expressed, was lower in rats with moderate degrees of insulin deficiency. On the other hand, LPL activity was comparable in all three groups of diabetic rats, and bore absolutely no relationship to the differences in TG concentration and kinetics that are self-evident in Table 1. Thus, the changes in plasma TG concentration that result from exercise training or diet cannot be attributed to variations in adipose tissue LPL activity.

The data in Figure 1 and Table 1 indicate that exercise training reduced the hyperglycemia and hypertriglyceridemia associated with a given degree of insulin deficiency in rats, and that the decrease in plasma TG concentration was associated with a fall in VLDL-TG secretion rate. An obvious explanation for all of these changes is that exercise training enhanced insulin action, thus promoting glucose utilization, inhibiting lipolysis, lowering plasma FFA concentration, and decreasing VLDL-TG secretion. Obviously, a decrease in plasma FFA concentration plays a central role in this formulation, and this hypothesis was evaluated in a second series of experiments. In these studies, we also evaluated the ability of exercise training to attenuate the effect of sucrose on plasma glucose and TG levels in insulin-deficient rats.

The results of the second series of experiments are seen in Figure 2, and the data in the left panel again demonstrate that exercise training ameliorated hyperglycemia ($P < 0.01$) and hypertriglyceridemia ($P < 0.05$) in chow-fed rats. Furthermore, it is clear that plasma FFA concentrations were significantly lower in exercise-trained rats ($P < 0.001$). Finally, plasma insulin levels were reduced to a similar degree in both groups of diabetic rats.

The data in the right panel of Figure 1 also indicate that exercise training dramatically reduced the severity of hyperglycemia ($P < 0.005$) and hypertriglyceridemia ($P < 0.01$) produced by feeding sucrose to insulin-deficient rats. Indeed, the effect of exercise training was more striking in sucrose-fed than in chow-fed rats. However, this may have been due to the fact that these sucrose-fed rats happened to be "good runners," and spontaneously ran an average of 6.98 miles/day as compared with a mean of 2.98 miles/day for chow-fed rats. Furthermore, the data in the right panel demonstrate that plasma FFA concentrations in sucrose-fed, exercise-trained rats with diabetes, were approximately one-third the value ($P < 0.001$) of diabetic, sucrose-fed, sedentary rats. However, insulin levels were similar in both groups of rats, and comparable to those of the chow-fed rats.

DISCUSSION

Moderate insulin deficiency in rats is associated with hyperglycemia and hypertriglyceridemia,[6,7,14] and the results of the studies presented indicate that exercise training ameliorated and sucrose feeding accentuated these metabolic defects. As such, these data emphasize the profound degree to which environmental factors can modulate the diabetic state.

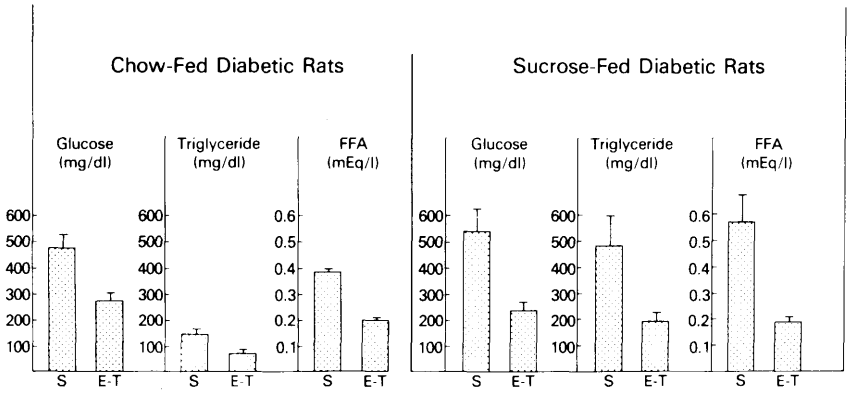

FIGURE 2. Effect of exercise on mean (±SEM) plasma glucose, triglyceride (TG), and FFA concentrations in chow-fed and sucrose-fed sedentary (S) and exercise-trained (ET) diabetic rats. The numbers in parentheses indicate the number of rats in each experimental group.

Before discussing the effects of diet and exercise training on VLDL-TG metabolism in rats with moderate insulin deficiency, it seems necessary to first discuss the mechanism of the hypertriglyceridemia seen in this situation. The data in Table 1 indicate that the elevation in plasma TG levels seen in sedentary diabetic rats occurs in the absence of any change in TG secretion rates. Thus, a defect in VLDL-TG catabolism must be responsible for the development of hypertriglyceridemia in insulin-deficient rats, a conclusion which is consistent with previously published data.[6,7,14] Furthermore, since sucrose-fed and chow-fed sedentary diabetic rats had similar TG secretion rates, the striking increase in plasma TG levels seen when sedentary diabetic rats are fed sucrose must be secondary to an accentuation of the defect in VLDL-TG catabolism already present in insulin-deficient rats.

The situation as regards the effect of exercise training on TG metabolism of insulin-deficient rats is more complicated. On the one hand, it is clear that the lowering of plasma TG levels in exercise-trained rats was associated with a fall in TG secretion rates. On the other hand, the magnitude of the fall in TG secretion rates may not be sufficient to account for the lowering of plasma TG concentrations. For example, mean TG secretion rates in exercise-trained diabetic rats was 70% of that in control rats. If the difference in TG concentrations between these two groups was solely due to differences in TG secretion rates, exercise-trained rats should have had a mean plasma TG concentration of 63 mg/dl (0.70 × 90 mg/dl), instead of 51 mg/dl. Similarly, mean TG secretion rate of exercise-trained diabetic rats was 72% of that seen in sedentary diabetic rats, and this should have led to a TG concentration of 92 mg/dl, not 51 mg/dl. The reason for this apparent discrepancy is not clear. It may simply be a reflection of the fact that the TG turnover studies are difficult to do, and one should not expect a better degree of correlation. Alternatively, it is possible that exercise training leads to an increase in TG catabolism, in addition to the reduction in TG secretion. Unfortunately, it is impossible to choose between these two possibilities at this time.

Although the fall in plasma TG levels associated with exercise training may not be due *entirely* to a reduction in TG secretion rates, it is clear that TG secretion rates were lower in exercise-trained rats. Since it has been shown that VLDL-TG secretion by perfused livers is directly related to perfusate FFA concentrations,[7,20] it seemed reasonable to speculate that the reduction in TG secretion rates and plasma TG concentrations seen in exercise-trained diabetic rats was secondary to a fall in plasma FFA levels. This possibility seemed particularly attractive in light of the evidence that the magnitude of hyperglycemia was also attenuated in exercise-trained diabetic rats. Therefore, it could be argued that exercise training enhances insulin-stimulated glucose uptake, thereby inhibiting lipolysis and lowering FFA concentrations. The data in Figure 2 indicate that exercise-trained diabetic rats did have lower plasma FFA, and that this was true of both chow-fed and sucrose-fed diabetic rats. Obviously, this formulation is based on the assumption that the primary effect of exercise training on TG secretion is to reduce the FFA flux to the liver, without affecting the pathway of de novo lipogenesis. Furthermore, the implication is that exercise training exerts a peripheral effect on intermediary metabolism, i.e., enhancing glucose uptake and reducing lipolysis, without having any direct action on hepatic TG metabolism. This point of view will require experimental verification, but we do have preliminary data which indicate that perfused livers from exercise-trained and sedentary rats increase TG secretion similarly in response to increases in perfusate FFA concentrations.

Finally, these data emphasize the uncertainty that still exists as to the mechanism of the defect in TG catabolism present in rats with insulin deficiency. In general, adipose tissue LPL activity has been found to be low in rats with insulin deficiency,[14,21–24] and this conclusion is supported by the data in Table 1. On the other hand, we have suggested that the decrease in adipose tissue LPL activity, either total or heparin-releasable, cannot account for the VLDL-TG catabolic defect associated with insulin deficiency.[14,24] As a result, we began searching for other mechanisms to explain the defect in VLDL-TG catabolism present in insulin-deficient rats, and recently described a factor present in the plasma of insulin-deficient rats which prolongs removal of TG when injected into normal rats.[25] Furthermore, plasma from sucrose-fed diabetic rats had a greater ability to prolong TG removal from the plasma of normal rats than did plasma from chow-fed diabetic rats. Thus, these observations can account for the fact that the VLDL-TG catabolic defect present in insulin-deficient rats is accentuated by a diet enriched in sucrose, in the absence of any change in adipose tissue LPL activity. However, before rejecting the possibility that reductions in LPL activity play a role in diabetic hypertriglyceridemia, it is essential to recognize the difficulty in assessing the functional activity of LPL. Presumably, adipose

tissue LPL activity reflects enzyme located both intra- and extracellularly, and it is difficult to know how best to assess the functional activity of the enzyme. Indeed, it could be argued that only the amount of LPL released into the plasma after heparin administration represents a relevant measurement of TG removal capacity. In that regard, it should be pointed out that circulating plasma levels of post-heparin LPL activity are not reduced in insulin-deficient rats.[26,27] Therefore, we would suggest that decreases in LPL activity associated with insulin deficiency may represent an epiphenomenon and be of relatively little importance in regulation of TG catabolism in insulin-deficient rats.

In conclusion, the data presented clearly demonstrate that exercise training and diet can modulate plasma TG concentrations and kinetics in rats with insulin deficiency. These results highlight the profound impact that environmental factors have on plasma TG concentrations in rats with moderate insulin-deficient diabetes, and raise important issues as to the treatment of diabetes in man.

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